July 23, 1999

VETERINARY SERVICES MEMORANDUM NO. 800.84

Subject: Guidelines for Submission of Materials in Support of Licensure

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

Supporting materials must accompany applications for a United States Veterinary Biologics Establishment License according to 9 CFR 102.3(a) and for a United States Veterinary Biological Product License according to 9 CFR 102.3(b). Applicants should submit these materials in packages that contain complete information whenever possible. The purpose of this memorandum is to define the contents of five submission packages, each containing the information and documents needed by APHIS to complete applicable licensing actions. This memorandum does not prevent license applicants from interacting with Center for Veterinary Biologics-Licensing and Policy Development (CVB-LPD) personnel on individual elements of an application package as necessary to facilitate submission, review, and licensure.

II. CANCELLATION

This memorandum cancels Veterinary Biologics Memorandum No. 800.84 dated July 26, 1995.

III. BACKGROUND

The review of applications for United States Veterinary Biologics Establishment Licenses and United States Veterinary Biological Product Licenses requires the submission and review of several individual items which have often been submitted on a piecemeal basis. APHIS' review and processing of license applications is more efficient, however, when submissions are more complete and contain all of the necessary materials to support a significant action to move the application forward. This memorandum identifies five data packages and the supporting materials that APHIS needs before taking a significant action on an application. Applicants' efforts to present supporting materials in complete packages as described here will help the Center for Veterinary Biologics to provide quality service.

IV. GUIDELINES FOR DATA PACKAGES

Applicants should submit materials in support of license applications to CVB-LPD in the five data packages described below. APHIS actions upon receipt of each package are also described.

A. Establishment License Application Package

1. *Contents of Establishment License Application Package* - Applicants should provide an application and all supporting materials required for an establishment license in one submission as follows:

a. Application for United States Veterinary Biologics Establishment License (APHIS Form 2001).

b. Articles of incorporation for the applicant and any subsidiaries if a corporation.

c. Water quality statement according to 9 CFR 108.11.

d. Application for at least one United States Veterinary Biological Product License (APHIS Form 2003 and accompanying Product License Application Package as described in part IV.B. below).

2. *Facilities Documents* - Concurrent with the submission of the Establishment License Application Package to CVB-LPD, the applicant should submit the following to the Center for Veterinary Biologics-Inspection and Compliance (CVB-IC):

a. Qualifications of supervisory personnel (APHIS Forms 2007) and

b. Blueprints, plot plans, and legends prepared according to 9 CFR 108.2-108.5.

3. *APHIS Actions on Establishment License Application Package*:

a. CVB-IC will conduct an inspection of the establishment prior to licensure after CVB-LPD has reviewed the Establishment License Application Package, a product license application, and the Outline of

Production and applicable special outlines and found them to be satisfactory.

b. CVB may only issue an establishment license after a product to be made in that establishment has qualified for licensure.

B. Product License Application Package

1. *Contents of Product License Application Package* - Applicants should submit a product license application with their preliminary supporting materials in one package as follows:

a. Application for United States Veterinary Biological Product License (APHIS Form 2003).

b. Outline of Production and special outlines, if applicable, according to 9 CFR 114.8-114.9.

c. Master Seed purity (freedom from extraneous bacteria, fungi, mycoplasma, and viruses), safety, and identity data for each Master Seed.

d. Master Seed characterization data for new live products and for recombinant-DNA derived products. These data should be adequate for APHIS to establish the proper containment requirements and to conduct confirmatory testing. For new live products and recombinant-DNA derived products, complete and submit (a paper copy and a copy in electronic format) the applicable portions of one of the following Summary Information Formats (available on the World Wide Web at: http//www.aphis.usda.gov/vs/cvb):

(1) Category I Veterinary Biologics,

(2) Category II Veterinary Biologics,

(3) Category III Veterinary Biologics,

(4) Conventionally Derived Veterinary Biologics, or

(5) Nucleic Acid-Mediated Vaccines.

e. Master Cell Stock (primary cells and cell lines) data on source and passage history, purity, and identity, according to 9 CFR 113.51 and 113.52.

f. Protocols for studies concerning host animal immunogenicity, safety, backpassage, shed/spread, interference, efficacy, and other studies.

2. *APHIS Actions on Product License Application Package:*

a. Review and process the Outline of Production and/or special outlines:

(1) If unsatisfactory, CVB-LPD will return the outline with comments.

(2) If satisfactory, CVB-LPD will file the outline pending receipt of satisfactory supporting data in the Product License Data Package (see C. below).

b. Review and comment on protocols for studies.

c. Review and file Master Seed and Master Cell Stock data:

(1) If satisfactory, CVB-LPD will request the submission of samples and the testing of Master Seed(s) and Master Cell Stock(s) at the Center for Veterinary Biologics-Laboratory (CVB-L).

(2) If unsatisfactory, CVB-LPD will file data with comments to the applicant concerning deficiencies and additional data needed.

d. CVB-LPD will authorize the firm to produce serials of product in production facilities after the results of Master Seed and Master Cell testing are satisfactory at CVB-L.

C. Product License Data Package

1. *Contents of Product License Data Package* - Applicants should submit additional data and materials needed to support the product license application in one package called the Product License Data Package. This package should

include the following data and supporting materials, as applicable to the product under consideration: (Note: The order of listing is not meant to reflect the sequence for conducting the required studies.)

a. General data supporting:

(1) Inactivation procedures for killed products,

(2) Maximum allowable moisture levels for desiccated products, and

(3) Other outline procedures as appropriate.

b. Product potency test data supporting:

(1) Sensitivity, specificity, and reproducibility of the test,

(2) Dose response, if applicable,

(3) Correlation with host animal protection,

(4) Reference qualification and stability, and

(5) Procedures for requalification and maintenance of the reference.

c. Host animal immunogenicity and efficacy data from:

(1) Any preliminary dose determination studies,

(2) Master Seed immunogenicity studies,

(3) Duration of immunity studies when applicable,

(4) Efficacy studies in maternal-antibody-positive animals when applicable, and

(5) Any other studies needed to support product label indications and recommendations.

d. Product safety data from studies in laboratory animals and contained host animals, including data to establish the safety of any new or significantly different adjuvant formulation.

e. Interference data when applicable.

f. Backpassage and shed/spread data when applicable.

g. Accelerated or other preliminary stability data.

h. Statistical analysis of data.

i. Completed APHIS Forms 2008 for satisfactory prelicensing serials of product (usually three consecutive serials).

j. Labels and/or label sketches.

k. Amended Outline of Production if the original outline was returned with comments in the review of the Product License Application Package.

2. *APHIS Actions on Product License Data Package:*

a. Review and file safety data.

(1) If satisfactory, CVB-LPD will request clearance of the adjuvant from FSIS, if applicable, and coordinate inspection of animals at slaughter, if needed.

(2) If unsatisfactory, CVB-LPD will provide comments to the applicant concerning deficiencies and additional data needed.

b. Review and file potency, efficacy, and other supporting data. If supporting data are unsatisfactory, CVB-LPD will provide comments to the applicant concerning deficiencies and additional data needed.

c. Review and file test results from prelicensing serials:

(1) If test results are satisfactory, CVB-LPD will authorize the firm to submit samples to CVB-L, and will request CVB-L to do prelicensing testing.

(2) If test results are unsatisfactory, CVB-LPD will request the applicant to produce and test additional prelicensing serials.

d. Review labels and/or label sketches:

(1) If labels are satisfactory, CVB-LPD will retain the labels with the file until the license is issued.

(2) If labels are unsatisfactory, CVB-LPD will process the labels as sketches with comments. CVB-LPD will process label sketches with or without comments as applicable.

e. Review the Outline of Production. CVB-LPD will file the outline as satisfactory or file it with comments requesting additional changes.

D. Field Test Request Package

1. *Contents of Field Test Request Package* - Applicants should submit requests to ship experimental veterinary biological products for field studies according to 9 CFR 103.3 in one package called the Field Test Request Package, which should include the following:

a. A permit or letter of authorization from proper State or foreign animal health authorities.

b. A tentative list of names of proposed recipients.

c. A description of the product, recommendations for use, and the results of preliminary research work, if not previously submitted in either the Product License Application or the Product License Data Package.

d. Labels for the experimental product.

e. The study protocol.

f. Data concerning the safety of the product, including safety in meat-producing animals, when applicable, if not previously submitted in a Product License Application Package.

g. A statement from the research investigator or research sponsor agreeing to provide additional information concerning each group of meat animals involved prior to movement of these animals from the premises where the test is to be conducted, when applicable.

h. A completed risk assessment to comply with NEPA. This applies to products not exempted by categorical exclusion from the preparation of an environmental assessment or an environmental impact statement by 7 CFR 372.5(c). The risk assessment should be based on the appropriate Summary Information Format (available on the World Wide Web at http://www.aphis.usda.gov/vs/cvb) for:

(1) Conventionally Derived Live Veterinary Biologics,

(2) Category II Veterinary Biologics,

(3) Category III Veterinary Biologics, or

(4) Nucleic Acid-Mediated Vaccines.

(Note: APHIS risk assessment procedures are described in "Risk Analysis for Veterinary Biologics" available from APHIS, CVB-LPD.)

2. *APHIS Actions on Field Test Request Package:*

a. Review and file information and data. If data and information are unsatisfactory, CVB-LPD will provide comment to the applicant concerning deficiencies and additional information or data needed.

b. When applicable, review the firm's risk assessment and complete the risk analysis process in accordance with "Risk Analysis for Veterinary Biologics" and NEPA requirements.

c. If data are satisfactory and NEPA requirements are satisfied, CVB-LPD will authorize shipment of the experimental product for field studies.

E. Field Test Data Package

1. *Contents of the Field Test Data Package* - Applicants should submit the results of field studies plus all additional supporting documents needed to

complete the product license application in one package called the Field Test Data Package. If applicable, this may include:

a. Field efficacy data,

b. Field safety data,

c. Final labels, if not previously submitted, and

d. Real-time stability data if available. If real-time data are not available, these data may be provided as a separate submission post-licensing.

2. *APHIS Actions on Field Test Data Package*:

a. Review and file data. If data are unsatisfactory, CVB-LPD will provide comments to the applicant concerning deficiencies and additional data needed.

b. Review the Labels:

(1) If labels are satisfactory, CVB-LPD will file them as final labels.

(2) If labels are unsatisfactory, CVB-LPD will file them as sketches with comments.

c. When applicable, review the firm's risk assessment and complete the risk analysis process according to "Risk Analysis for Veterinary Biologics" and NEPA requirements. An additional environmental assessment (EA) and finding of no significant impact (FONSI) will not be required prior to licensing the product if field test data support the conclusions of the EA and FONSI prepared prior to approval of the field test.

d. Issue a product license and, if applicable, an establishment license upon completion of all applicable requirements.

V. RESPONSE TO MATERIALS REVIEWED WITH COMMENTS

When APHIS provides comments when reviewing materials in a package, firms should combine any additional data and amended supporting materials needed to address the comments in one complete follow-up submission. If APHIS action does not depend upon the receipt of these materials, include these materials as part of a subsequent package that is submitted in support of the application. This helps to minimize the number of submissions needed to complete the licensing process.

VI. PRESENTATION OF DATA

As in any scientific work, reports of test results should include an introduction defining the subject and indicating the studies and trials which have been carried out. Applicants should note and justify any omission of indicated tests or information from a package.

A. Format for Reports

Applicants should report each study or trial undertaken with details given under the following headings in the following order:

1. *Title of the Study or Trial* - Include a reference number.

2. *Introduction* - Include a statement of the aim of the study or trial.

3. *References* - Refer to relevant Standard Requirements, Outlines of Production, or approved protocols.

4. *Names of Persons and Research Laboratories Involved in the Study*

5. *Dates of Start and End of the Study or Trial*

6. *Summary*

7. *Materials and Methods*

8. *Results*

9. *Discussion*

10. *Conclusions*

B. Bibliography

Applicants should provide a list and copies of all bibliographic references cited in support of their application.

VII. SUBMISSION OF DATA

Submit license applications and supporting materials prepared in packages as described in this memorandum to:

Center for Veterinary Biologics
Licensing and Policy Development
510 South 17th Street. Suite 104
Ames, IA 50010-8197

/s/ Thomas E. Walton for

Alfonso Torres
Deputy Administrator
Veterinary Services

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